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Continuous, transcutaneous oxygen tension measurements in experiments with Rhesus monkeys and pregnant ewes

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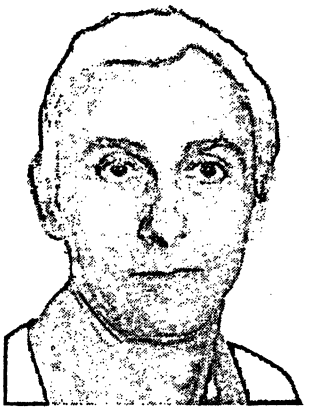
1 Introduction

After the first report by HUCH, HUCH, MEINZER and LÜBBERS on transcutaneous measurements of oxygen tension several papers describing this or similar electrodes based on the CLARK principle have been published [1, 3, 4, 12, 15, 18]. The technique has mainly been tested in perinatal medicine, but also in adults [7, 8, 13]. A publication on intrapartum registrations of human fetuses in considerable numbers came in 1977 [6], but other mainly preliminary reports have appeared during the last years [5, 12, 16]. From studies of newborn infants and adults it is knows that the correlation between intraarterial (PaO_2) and transcutaneous oxygen tension ($tcPO_2$) is high provided the peripheral circulation is adequate. Several investigors have found that at PaO_2 levels of 50 mm Hg (6.5 kPa) and higher the transcutaneous measuring system works well and gives correct information about PaO_2 changes, moreover predicts the PaO_2 level with good reliability. Coefficients of correlation of 0.9 or higher have been reported [2, 9, 10, 11, 13, 14, 17]. Although the CLARK electrode is linear from zero to more than 1000 mm Hg (135 kPa) it is not known if the correlation between PaO_2 and $tcPO_2$ is equally high at fetal levels when the pressure gradient for oxygen from the arterialized capillary blood to the $tcPO_2$ electrode is small. We have therefore studied the reliability of the electrode system in vivo at fetal PaO_2 levels. Moreover, as only one study [18] refers to animals with a skin quality different from human skin we also wanted to test the electrode system under specified conditions in two animal species often used in perinatal experiments.

Curriculum vitae



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2 Material and methods

Series 1: Juvenile Rhesus monkeys weighing 3–4 kg and about one year old were investigated. A total of six monkeys were exposed to the experimental procedure and of these four were included in the correlation studies. One animal was exposed to the procedure twice with an interval of one month. Two were excluded because of technical problems. The animals were anaesthetized with ketamin (Ketalar®) and pavulon (Pavulon®). They were

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intubated and ventilated by an Engström respirator and given different mixtures of oxygen and nitrous oxide. Arterial blood sampling and continuous monitoring of blood pressure with a Statham pressure transducer was made through a soft catheter introduced 20–25 cm proximally into a femoral artery. Heart rate was monitored from the ECG with a Corometric Neonatal Monitor 512.

Transcutaneous PO_2 was continuously recorded with an electrode manufactored by HUCH, University of Marburg and the electronic unit was developed by the Department of Electronic Development, University of Marburg. Calibration was performed in air, nitrogen and a gas mixture of about 4% oxygen in nitrogen. Duplicate analyses of oxygen tension in arterial blood samples were kindly performed by the Department of Clinical Physiology using a Radiometer BMS 3Mk2 blood micro system and a Radiometer digital acid-base analyzer PHM72. This equipment was calibrated for the PO_2 measurements with nitrogen and a gas mixture of 12% oxygen in nitrogen. Duplicate determinations of the PaO_2 had a coefficient of variation of 0.7%.

The transcutaneous electrode was fixed with an acrylat glue (Loctite IS415) to the skin in the inguinal region after local shaving and rubbing with sandpaper untill the skin almost bled. Only after such preparations did we find the same response on time in the $tcPO_2$ electrode system as in recordings of human fetuses or newborn infants.

Using this experimental design the animals were exposed to repeated periods of hypoxia by lowering the oxygen concentration of the inhaled gas mixture. During each period an attempt was made to lower PaO_2 to levels below 50 mm Hg (6.5 kPa) and to maintain this level long enough to achieve stable recordings of $tcPO_2$ at the lowest possible oxygen level. After each session the animals were ventilated with 100% oxygen in order to reestablish circulatory balance as fast as possible.

Series 2: A second series of experiments was performed on four pregnant ewes near term. The animals were anaesthetized and ventilated as in the first series. The hind legs and the breech of the fetus were delivered through a corporal hysterotomy. A soft catheter was introduced into a femoral artery of the fetus for blood sampling and continuous recording of arterial blood pressure. Monitoring of heart rate was performed as in the monkey experiments. The oxygen electrode was applied on the trunk of the fetus with glue after local shaving. The fetus was then replaced into the uterus and the hysterotomy closed. The maternal circulatory condition was monitored by continuous recording of ECG and arterial blood pressure via a catheter introduced into a carotid artery. Maternal and fetal blood was sampled during periods of normoxia and hypoxia brought about by lowering the oxygen levels in the inhaled gas mixture.

3 Results

The correlation between PaO_2 and $tcPO_2$ in the monkey experiments is presented in Tab. I.

Values were accepted in the correlation study only when the $tcPO_2$ recording showed stable levels. To achieve this in a reasonable period of time the PaO_2 had to be lowered in steps of not more than 50 mm Hg (6.5 kPa).

The mean of the absolute difference between PaO_2 and $tcPO_2$ was 9.0 mm Hg (1.20 kPa). The standard deviation was 6.1 and the range of the differences 1–23 mm Hg (0.13–3.07 kPa). At values below 50 mm Hg (6.5 kPa) the differences ranged from 2–18 mm Hg (0.26–2.40 kPa).

The correlation between PaO_2 and $tcPO_2$ in the monkey series is presented in Fig. 1. The coefficients of correlation was high, varying from 0.91 to 0.99 with a slope ranging from 0.77 to 1.26 and a intercept from –0.4 to 14.5 mm Hg (0.52 respectively 1.89 kPa). The numbers of observations in each animal was between 3 and 7.

In some cases an impaired circulation was observed with hypotension and decreasing pulse amplitude. A typical example is illustrated in Fig. 2. Then $tcPO_2$ rapidly decreased resulting in increased discrepancy between central PaO_2 and the $tcPO_2$. To study the importance of this phenomenon we constructed $tcPO_{2x}$, defined as the extrapolated $tcPO_2$ 45 seconds after the arterial blood sampling. The interval of 45 seconds was chosen as an average value for the delay in the functional unit, skin-electrode. The differences between recorded and extrapolated $tcPO_2$ were however small and statistically not significant.

Tab. I. Correlation between PaO_2 and $tcPO_2$ in the monkey experiments

Monkey no.	PaO_2	$tcPO_2$	$tcPO_2-PaO_2$	ratio $\frac{PaO_2}{tcPO_2}$
1	44 (5.9)	51 (6.8)	7 (0.9)	0.9
	16 (2.1)	18 (2.4)	2 (0.3)	0.9
	22 (2.9)	26 (3.5)	4 (0.5)	0.9
	23 (3.1)	25 (3.3)	2 (0.3)	0.9
2	65 (8.7)	85 (11.3)	20 (2.7)	0.8
	41 (5.5)	51 (6.8)	10 (1.3)	0.8
	41 (5.5)	56 (7.5)	15 (2.0)	0.7
	33 (4.4)	51 (6.8)	18 (2.4)	0.7
	21 (2.8)	27 (3.6)	6 (0.8)	0.8
3	51 (6.8)	74 (9.7)	23 (3.1)	0.7
	24 (3.2)	39 (5.2)	15 (2.0)	0.6
	49 (6.5)	56 (7.5)	7 (0.9)	0.9
	24 (3.2)	41 (5.5)	17 (2.3)	0.6
	55 (7.3)	56 (7.5)	1 (0.1)	1.0
	23 (3.1)	18 (2.4)	−5 (0.7)	1.3
	97 (12.9)	93 (12.4)	−4 (0.5)	1.0
4	81 (10.8)	72 (9.6)	−9 (1.2)	1.1
	23 (3.1)	17 (2.3)	−6 (0.8)	1.4
	20 (2.8)	33 (4.4)	13 (1.7)	0.6
1 (2nd experiment)	34 (4.5)	37 (4.9)	3 (0.4)	0.9
	62 (8.3)	69 (9.2)	7 (0.9)	0.9
	29 (3.9)	40 (5.3)	11 (1.5)	0.7
	53 (7.1)	65 (8.7)	12 (1.6)	0.8
	32 (4.3)	37 (4.9)	5 (0.7)	0.9
	29 (3.9)	32 (4.3)	3 (0.4)	0.9

PO_2 values are given in mm Hg, in kPa in brackets

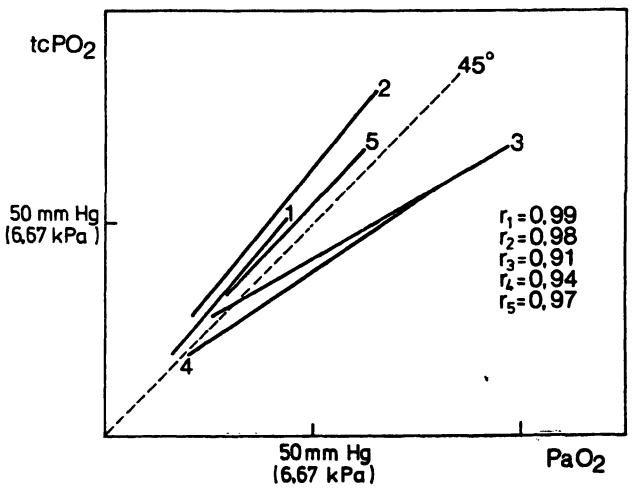

Fig. 1. The individual lines of correlation between PaO_2 and $tcPO_2$ in the interval of observed PaO_2 in the monkey series.

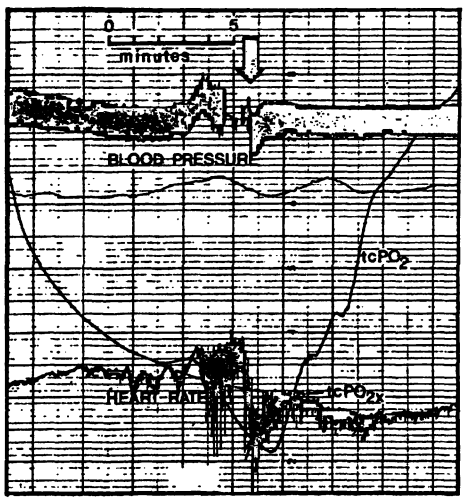

Fig. 2. Example of the extrapolated $tcPO_2$. The dotted line refers to the extrapolation. Time of blood sampling is marked with an arrow. The impaired circulation is demonstrated by a primary rise followed by a marked decline both in arterial blood pressure and heart rate.

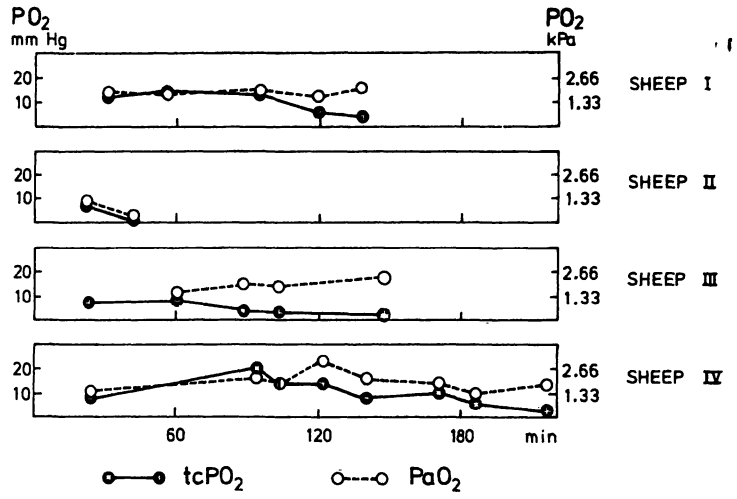

Fig. 3. PaO_2 and $tcPO_2$ in the four fetal lamb experiments. Note the increasing discrepancy between PaO_2 and $tcPO_2$ with length of experimental procedure. No reapplication of the $tcPO_2$ electrode was carried out in this series.

The results from the fetal lamb series are shown in Fig. 3. As seen we found a good agreement between PaO_2 and $tcPO_2$. The length of the recording was however of great importance as the discrepancy between PaO_2 and $tcPO_2$ began to increase with time, usually most prominent after 2–3 hours.

4 Discussion

Our investigations demonstrates that the transcutaneous oxygen tension electrode is a useful tool for continuous monitoring of the arterial oxygen tension in monkey and fetal sheep experiments when preparations are performed as described. The response time in the functional unit, skin-electrode, is then roughly of the same order as in measurements on man. Changes in the transcutaneous oxygen tension recording were consistently parallel to changes in the arterial oxygen tension. Even at fetal levels the correlation between PaO_2 and $tcPO_2$ was high provided the peripheral circulation was adequate. It was however not possible to predict changes in arterial oxygen tension quantitatively correct in all situations. In some cases the ratio $PaO_2/tcPO_2$ was fairly constant throughout the experiment (see no. 1, 2 and 5 in Tab. I). The ratio from the first set of values may when be used as a constant by which a recorded $tcPO_2$ value can be multiplied to give a better estimate of the actual PaO_2. Unfortunately the ratio may in other cases (see no. 3 and 4 in Tab. I) show considerable variations from values below one to values over one. This makes attempts to readjust the in vitro calibration from a set of values found in vivo unreliable. It should however be remembered that the PaO_2 changes are faster than the $tcPO_2$ changes. Small and rapid changes in PaO_2 thus may not be revealed in $tcPO_2$. Another possible explanation to the discrepancy in experiment three and four in the monkey series may be unobserved technical problems in the anaerobic sampling of arterial blood. The rapidity of the reaction in the electrode system and the correlation between PaO_2 and $tcPO_2$ seems to decrease with the length of time in experimental procedures and the $tcPO_2$ electrode should be reapplied after 2–3 hours.

Summary

Several papers describing electrodes for transcutaneous measurements of oxygen tension based upon the CLARK principle have been published during the last years. The technique has mainly been testes in perinatal medicine but in 1977 came the first report on intrapartum registrations on human fetuses in a considerable number. From studies

in adults and newborn infants it is known that at oxygen tension levels of 50 mm Hg (6.5 kPa) or higher the transcutaneous measuring system works well and gives correct information about arterial PaO_2 changes, moreover predicts the PaO_2 level with good reliability provided the peripheral circulation is adequate. To study the correlation in vivo at low, fetal levels of PaO_2 and, to a certain extent, test the $tcPO_2$ electrode system in animals often used in perinatal experiments but with skin quality different from human skin we performed two series of experiments, one with four juvenile Rhesus monkeys, one with the fetuses of four pregnant ewes near term. The animals were anaesthetized and ventilated with respirator. Continuous monitoring of heart rate, blood pressure and transcutaneous oxygen tension was performed, the latter intrauterine in the sheep series. The results of the correlation study in the monkey series are presented in table 1. **The mean of the absolute difference between PaO_2 and $tcPO_2$ was 9.0 mm Hg (1.20 kPa), the standard deviation 6.1 mm Hg (0.81 kPa)** and the range of the differences 1–23 mm Hg (0.13–3.07 kPa). The agreement between PaO_2 and $tcPO_2$ were about the same at fetal as at higher PO_2 levels. The correlation between PaO_2 and $tcPO_2$ was high. The individual coefficients of correlation in the monkey experiments varied from 0.91 to 0.99 (see Fig. 1). Also in the fetal sheep series there was a good accordance between PaO_2 and $tcPO_2$. **If the monitoring lasted longer than 2–3 hours we found an increasing discrepancy between PaO_2 and $tcPO_2$ (see Fig. 3).**

The studies demonstrated that the transcutaneous oxygen tension electrode is a usefull tool for continuous monitoring of the arterial oxygen tension in monkey and fetal sheep experiments when preparations are performed as described. The response time in the functional unit, skin-electrode, is then of the same magnitude as in man. Changes in the transcutaneous oxygen tension recording were consistently parallel to changes in arterial oxygen tension. Even at fetal levels the correlation between PaO_2 and $tcPO_2$ was high provided the peripheral circulation was adequate. It was however not possible to predict changes in arterial oxygen tension quantitatively correct in all situations. It should be remembered that the PaO_2 changes are faster than the $tcPO_2$ changes. **Small and rapid fluctuations in PaO_2 thus may not be revealed in $tcPO_2$.** Another possible explanation to unexpected discrepancy between PaO_2 and $tcPO_2$ may be unobserved technical problems in the anaerobic sampling of arterial blood. **The rapidity of the reaction in the electrode system and the correlation between PaO_2 and $tcPO_2$ seems to decrease with the length of time in experimental procedures and the $tcPO_2$ electrode should be reapplied after 2–3 hours.**

Keywords: Animal experiments, oxygen tension, transcutaneous measurements

Zusammenfassung

Kontinuierliche, transkutane Messung der Sauerstoffspannung in Experimenten mit Rhesusaffen und schwangeren Mutterschafen.

Während der letzten Jahre wurden zahlreiche Arbeiten veröffentlicht, in denen Elektroden zur transkutanen Messung der Sauerstoffspannung beschrieben wurden. Die Methodik basierte auf dem CLARK-Prinzip. Nachdem die Technik hauptsächlich in der perinatalen Medizin zur Anwendung kam, erschienen 1977 erste Berichte zur Messung der Sauerstoffspannung an einer beträchtlichen Anzahl menschlicher Feten. Aus Untersuchungen an Erwachsenen und Neugeborenen ist bekannt, daß bei einer Sauerstoffspannung von 50 mm Hg und höher das transkutane Meßsystem gut funktioniert. Es liefert in der Tat richtige Informationen über Schwankungen des arteriellen O_2-Partialdruckes; darüberhinaus läßt sich der pO_2-Wert selbst mit guter Verläßlichkeit prognostizieren, unter der Voraussetzung, daß die periphere Zirkulation adäquat funktioniert. Um nun die Korrelation in vivo bei fetalem, sprich niedrigem Sauerstoff-Partialdruck zu untersuchen und, bis zu einem gewissen Grad, das transkutane pO_2-Elektrodensystem an Tieren auszutesten, die häufig in perinatalen Experimenten Verwendung finden, sich aber doch hinsichtlich ihrer Hautbeschaffenheit vom Menschen unterscheiden, führten wir zwei Untersuchungsserien durch: eine Serie mit 4 juvenilen Rhesusaffen und eine zweite an Feten von 4 Mutterschafen nahe am Termin. Die Tiere wurden anästhetisiert und mit einem Respirator ventiliert. Kontinuierlich wurden Herzfrequenz, Blutdruck und transkutane Sauerstoffspannung aufgezeichnet; die Messung der Sauerstoffspannung erfolgte bei der Schaf-Serie intrauterin. Die Ergebnisse der Korrelationsberechnung in der Affen-Serie sind in Tab. 1 dargestellt. **Die mittlere absolute Differenz zwischen pO_2 und transkutanem pO_2 betrug 9.0 mm Hg bei einer Standardabweichung von 6.1 mm Hg.** Die absoluten Werte lagen zwischen 1 und 23 mm Hg. Übereinstimmungen zwischen pO_2 und transkutanem pO_2 waren bei den fetalen wie bei den höheren pO_2-Werten ungefähr gleich: **es ergab sich eine hohe Korrelation zwischen pO_2 und transkutanem pO_2.** Auf jedes einzelne Tier im Affenexperiment bezogen, wurden Korrelationskoeffizienten gefunden, die von 0.91 bis 0.99 rangierten (Fig. 1).

Auch bei den Schaf-Feten wurde eine gute Übereinstimmung zwischen pO_2 und transkutanem pO_2 gefunden. **Jedoch stellten wir bei Messungen, die über einen Zeitraum von 2–3 Stunden hinausgingen, eine zunehmende Diskrepanz zwischen den untersuchten Größen fest** (Fig. 3).

Die Untersuchungen zeigten uns, daß die transkutane Meßelektrode ein brauchbares und nützliches Mittel zur Aufzeichnung der arteriellen Sauerstoffspannung darstellt. Das gilt sowohl für die untersuchten Rhesusaffen wie auch für die Schaf-Feten unter der Voraussetzung, daß die Versuche wie oben beschrieben durchgeführt werden. Die Reaktionszeit der funktionellen Einheit „Haut-Elektrode" ist somit von derselben Geschwindigkeit wie beim Menschen. Veränderungen, die durch die Elektrode angezeigt wurden, entsprachen den parallel erfolgten Änderungen der arteriellen Sauerstoffspannung. Selbst bei den Werten auf fetalem Niveau ergab sich eine hohe Korrelation zwischen pO_2 und transkutanem pO_2, natürlich unter

der Voraussetzung einer adäquaten peripheren Zirkulation. Es war jedoch nicht möglich, quantitative Veränderungen der arteriellen Sauerstoffspannung in jeder Situation ganz korrekt zu prognostizieren. Man muß daran erinnern, daß pO_2-Schwankungen schneller erfolgen als transkutane pO_2-Änderungen; kleine und schnelle Fluktuationen im pO_2 müssen sich deshalb nicht im transkutanen pO_2 niederschlagen. Eine andere mögliche Erklärung für unerwartete Diskrepanzen zwischen pO_2 und transkutanem pO_2 könnte in bislang nicht realisierten, technischen Problemen liegen, z. B. das anaerobe Sampling des arteriellen Blutes. Die Reaktionsschnelligkeit des Elektrodensystems sowie die Korrelation zwischen pO_2 und transkutanem pO_2 scheint mit der Länge der Versuchsdauer abzunehmen; die transkutane pO_2-Elektrode sollte deshalb nach 2 bis 3 Stunden ersetzt werden.

Schlüsselwörter: Sauerstoffspannung, Transcutane Messung, Tierversuche

Résumé

Mesures expérimentales, continues et transcutanés de la tension d'oxygène sur des singes rhésus et des brebis gravides

Plusieurs articles décrivant les électrodes utilisées pour les mesures transcutanées de tension d'oxygène basées sur le principe de CLARK ont été publiés au cours des dernières années. La technique a été principalement expérimentée en médecine périnatale, mais c'est en 1977 que sortit le premier rapport relatif aux enregistrements intrapartum sur un grand nombre de foetus humains. Nous savons d'études réalisées sur des adultes et des nouveaux-nés que pour des degrés de tension d'oxygène de 50 mm Hg (6,5 kPa) ou plus, le système de mesure transcutanée fonctionne bien et fournit des informations exactes sur les changements de PaO_2 artériel et que, de plus, il donne à l'avance le niveau de PaO_2 avec un taux faible d'erreur à condition que la circulation périphérique soit conforme. Pour étudier la corrélation in vivo à des niveaux foetaux bas de PaO_2 et tester jusqu'à un certain degré le système d'électrode $tcPO_2$ chez les animaux souvent utilisés dans les expérimentations périnatales mais avec une qualité cutanée autre que chez l'être humain, nous avons effectué deux séries d'expériences, l'une avec quatre singes rhésus jeunes, l'autre avec les foetus de quatre brebis gravides et proches du terme. Les bêtes ont été anesthésiées et ventilées au respirateur. On a assuré l'enregistrement continu de la fréquence cardiaque, de la tension sanguine et de la tension d'oxygène transcutanée, cette dernière de façon intrautérine dans la série ovine. Les résultats de l'étude de corrélation dans la série des singes figurent au tab. 1. **La moyenne de la différence absolue entre PaO_2 et $tcPO_2$ a été de 9,0 mm Hg (1,20 kPa), la déviation standard de 6,1 mm Hg (0,81 kPa)** et la courbe des différences de 1 à 23 mm Hg (0,13–3,07 kPa). La concordance entre le PaO_2 et le $tcPO_2$ a été à peu près identique pour les degrés de PO_2 foetaux et supérieurs. **La corrélation entre PaO_2 et $tcPO_2$ s'est montrée élevé.** Les coefficients individuels de corrélation dans les expériences de singes ont varié de 0,91 à 0,99 cf. fig. 1). De même, dans la série des foetus de brebis, on a pu observer une bonne concordance entre le PaO_2 et le $tcPO_2$. **Dans les cas où l'enregistrement a dépassé 2–3 h., nous avons relevé un écart croissant entre le PaO_2 et le $tcPO_2$** (cf' fig' 3).

Les études ont démontré que l'électrode de tension d'oxygène transcutanée est un instrument utile pour l'enregistrement continu de la tension d'oxygène artérielle dans les expériences de singe et de mouton foetal quand les préparations sont appliquées selon les descriptions données. Le temps de réponse dans l'unité fonctionnelle, l'électrode cutanée, est alors de la même amplitude que chez l'être humain. Des changements dans l'enregistrement de la tension d'oxygène transcutanée ont suivi une parallèle constante aux changements de la tension d'oxygène artérielle. Même aux niveaux foetaux, la corrélation entre le PaO_2 et le $tcPO_2$ s'est montrée élevée quand la circulation périphérique était conforme. Cependant, il n'a pas été possible de prédire des changements dans la tension d'oxygène artérielle quantitivement correcte dans toutes les situations. Il importe de rappeler que les changements du PaO_2 sont plus rapides que ceux de $tcPO_2$, d'où il peut arriver que **les fluctuations faibles et rapides du PaO_2 n'apparaissent pas dans le $tcPO_2$**. Une autre explication possible de l'écart surprenant entre le PaO_2 et le $tcPO_2$ pourrait résider dans des problèmes techniques non apparents dans l'échantillonnage anaérobien du sang artériel. **La rapidité de la réaction dans le systéme d'electrodes et la corrélation entre le PaO_2 et le $tcPO_2$ semblent décroître avec l'étendue du temps dans les processus expérimentaux et l'électrode de $tcPO_2$ devrait être appliquée à nouveau après 2–3 heures.**

Mots-clés: Expériences animales, mesures transcutanées, Tension d'oxygène

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